Pancreatic intraepithelial neoplasia (PanIN)

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Precursor lesions of invasive pancreatic cancer

- Pancreatic intraepithelial neoplasms (PanINs) – precursors of pancreatic ductal adenocarcinoma (PDAC)
- Mucinous cystic neoplasms (MCN)
- Intraductal papillary-mucinous neoplasms (IPMN)
Pancreatic ductal adenocarcinoma

- represents 85-90% of all pancreatic neoplasms
- the incidence almost equals the mortality rate
- 4th leading cause of cancer related death
- increasing incidence, 5-year survival under 5%
- no early signs and symptoms = late diagnosis
- absence of effective screening; early diagnosis (preinvasive stages)
- understanding the precursor lesion: identification of markers for early detection, targets for chemoprevention and therapy
■ **PanIN:**
- microscopic precursor of PDAC

■ **IPMN a MCN:**
- macroscopic cystic precursor lesion of IPM carcinoma and mucinous cystadenocarcinoma ("pancreatic incidentaloma" – asymptomatic cysts and/or dilatation of main ducts)
Pancreatic intraepithelial neoplasms

- non-invasive intraductal epithelial proliferation
- three grades (PanIN-1A and 1B; 2; 3): based on the architecture and cytonuclear atypia
  - PanIN-1A: mucinous cell hyperplasia (flat)
  - PanIN-1B: ductal papillary hyperplasia
  - PanIN-2: any PanINs with moderate dysplasia (usually papillary)
  - PanIN-3: severe ductal hyperplasia; carcinoma in situ
Pancreatic intraepithelial neoplasms

- PanIN-1A
- PanIN-1B
- PanIN-2
- PanIN-3
PanIN lesions: low grade vs high grade
Oncogenesis of pancreatic ductal adenocarcinoma: current accepted linear model of progression.

- Activation of oncogenes
  - KRAS, MYB, AKT2, AIB1
- Inactivation of tumor suppressor genes
  - p16, TP53, DPC4, BRCA2, LKB1/STK11
- DNA Mismatch Repair
  - MSH2, MLH1,....
- Epigenetic alterations, dysregulation of oncoproteins, activation of Hedgehog and Notch signalling pathways

<table>
<thead>
<tr>
<th></th>
<th>PanIN-1A</th>
<th>PanIN-1B</th>
<th>PanIN-2</th>
<th>PanIN-3</th>
<th>Karzinom</th>
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<tbody>
<tr>
<td><strong>activation K-ras</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ (75-90 %)</td>
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<tr>
<td><strong>inactivation p53</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+ (50-75 %)</td>
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<tr>
<td><strong>inactivation p16</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ (85-95 %)</td>
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<tr>
<td><strong>inactivation DPC4</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+ (45-55 %)</td>
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<td><strong>inactivation BRCA2</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+ (7-10 %)</td>
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<tr>
<td><strong>overexpression/amplification AKT2</strong></td>
<td></td>
<td></td>
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<td>+</td>
<td>+ (10-15 %)</td>
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<tr>
<td><strong>overexpression/amplification AIB1</strong></td>
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<td>+ (10-20 %)</td>
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<td><strong>overexpression/amplification MYB</strong></td>
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<td>+ (10 %)</td>
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<td><strong>mutation hMLH1/hMSH2</strong></td>
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<td>+ (4 %)</td>
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<td><strong>activation Hedgehog and Notch</strong></td>
<td></td>
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<tr>
<td><strong>overexpression EGFR, VEGF</strong></td>
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<td>+ (70 %)</td>
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<td><strong>overexpression/amplification HER-2</strong></td>
<td></td>
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<td>+ (16-20 %)</td>
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<tr>
<td><strong>overexpression cyclin D1, Ki67</strong></td>
<td></td>
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<td><strong>aberrant expression of 5-LOX and COX-2</strong></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+ (56-90 %)</td>
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<tr>
<td><strong>aberrant expression of PSCA, MUC1,4,5, fascin, claudin18, S100P</strong></td>
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<tr>
<td><strong>aberrant expression of mesothelinu</strong></td>
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<td>+</td>
<td>+ (55 %)</td>
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</table>
- **K-ras mutations in PanINs**: in all grades of PanINs
- **LOH analysis of p16, p53, DPC4**: rising incidence of LOH in increasing PanIN grade: decisive step: p53 and DPC4 tumor suppressor genes inactivation → **PanIN-2**: first truly preneoplastic stage in PDAC progression
- **Shortening of telomeres**: in all grades of PanINs (predisposes PanINs to accumulate progressive chromosomal abnormalities)
- **No marker that identifies only risky high-grade PanINs.**
PanINs in pancreatic cancer

- all grades of PanINs observed in pancreatic resection specimens with PDACs and their variants
- low-grade PanINs diffusely distributed within the pancreas
- high-grade PanINs in the vicinity of infiltrating tumors
  - independent PanINs (clonal heterogeneity between PanINs and the corresponding PDAC)
  - intraductal growth of PDAC (cancerization of the ducts)
- PanINs (usually low-grade) also found in resection specimens with ACCs, MCNs, serous adenomas, SPT, pancreatic endocrine tumors
PanIN lesions in chronic pancreatitis (CP)

- PanINs observed in normal pancreata and also in CP
- PanINs more frequently present in CP than in normal pancreata in about 40-60 % of pancreata with CP
- Majority of PanINs in CP: low grade PanINs; localized in the head of the pancreas (not confirmed by all studies)
- PanIN-3 lesions in <5% of such pancreata (not confirmed by all studies)
- Age and duration of CP did not correlate with the grade of PanINs and their K-ras status
- Alteration of tumor suppressor p16 (e.g. hypermethylation of the p16 promoter) demonstrated in significant number of PanINs in CP: contribution to cancer progression in CP
- PanINs: a possible link between CP and PDAC
Pancreatic inflammation in pancreatic carcinogenesis

- Production of reactive oxygen species (ROS), cytokine release, and upregulation of pro-inflammatory transcription factors
- Suppression of inflammation and oxidative damage: chemoprevention and treatment of PDAC
- Mediators of the inflammatory pathways (e.g., NF-κB, COX-2, 5-LOX, IL-8, ...):
  - Induce genetic damage
  - Promote cell proliferation
  - Inhibit apoptosis
  - Regulate the tumor associated angiogenesis
Alternative hypothesis for PDAC progression (non-linear)

- PanIN-1 lesions may follow a progression route different from PanIN-2/3
- PanINs-1: lead to growth arrest (?K-ras mutations in normal cells?)
- PanINs-2/3: ?K-ras mutation in cells with LOH at tumor suppressor loci?

Natural history of PanINs

- **linear progression from low- to high grade PanINs**
  - the time axis long
  - low-grade PanINs existing for years
  - sequence of genetic alterations (K-ras + p16, p53, DPC4) resulting in high-grade PanINs and progression into PDAC

- **de novo high-grade PanINs associated with low-grade PanINs**
  - the time axis short
  - rapid progression into PDAC
  - role of low-grade PanINs unclear

PanINs and the development of PDAC (cell of origin)

- **Ductal cells (histogenetical classification concept)**
  - Small or large ducts
  - Centroacinar units

- **Stem cells (stem cell concept)**
  Cells with stem cells properties → cancer stem cells → cancer

  - Nestin expressing progenitors: the compartment of origin for PanIN (Carriere et al. PNAS 2007; 104:4437-4442)
Knowledge of precursor lesions

- PanINs – precursors of PDAC
- precursor lesions: the tool for understanding of molecular basis of the disease
- identification of potential biomarkers for early detection of pancreatic cancer
- targets for chemoprevention and therapy of pancreatic cancer
Thank you for your attention....